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Synthesis and carbonic anhydrase inhibitory properties of novel cyclohexanonyl bromophenol derivatives

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ABSTRACT

The Naturally occurring novel cyclohexanonyl bromophenol 2(*R*)-2-(2,3,6-tribromo-4,5-dihydroxybenzyl)cyclohexanone (**4**) was synthesized as a racemic compound. Cyclohexylphenyl methane derivatives (**10–17**) with Br, OMe, CO, and OH were also obtained. Inhibition of four human carbonic anhydrase (hCA, EC 4.2.1.1) isozymes I, II, IV, and VI, with compounds **2–4, 8**, and **10–26** was investigated. These compounds were found to be promising carbonic anhydrase inhibitors and some of them showed interesting inhibitory activity. Some of the compounds investigated here showed effective hCA inhibitory activity, and might be used as leads for generating novel carbonic anhydrase inhibitors which are valuable drug candidates for the treatment of glaucoma, epilepsy, gastric and duodenal ulcers, neurological disorders, and osteoporosis.

Natural bromophenols, frequently isolated from red algae of the family Rhodomelaceae, have prominent biological activities.[1] Among these natural compounds, **1** exhibits isocitrate lyase[1c] and microbial[1d–f] activities. The other natural compounds **2** and **3** show significant aldose reductase inhibitory activities (Fig. 1).[1f] Additionally, it was reported that phenolic natural[1g] and synthetic dopaminergic[2] compounds are inhibitors of human carbonic anhydrases. Antioxidant activities of **1** and **3** have also been reported.[1h,i] Choi and co-workers reported the isolation of natural bromophenol 2(*R*)-2-(2,3,6-tribromo-4,5-dihydroxybenzyl)cyclohexanone (**4**) and its antioxidant property.[1f]

The carbonic anhydrases (CA; carbonate hydrolyase, EC 4.2.1.1) are a ubiquitous family of zinc-containing enzymes, that classically participate in the maintenance of pH homeostasis in the human body, catalyzing the reversible hydration of carbon dioxide in a two-step reaction to yield bicarbonate and protons.[2] The enzyme plays an important role in physiological anion exchange processes.[2a] At least 16 CA isozymes have been described to date in mammals, the most active ones as catalysts for carbon dioxide hydration being CA II.[3,4] CA II is found primarily in red blood cells but also in many other secretory tissues of the kidney, lung, eye, etc.[2,3] Carbonic anhydrase VI (CA VI) is a secretory enzyme that was initially described in the ovine parotid gland, and saliva, and normal human serum.[3b] Other CA isoforms are found in a variety of tissues where they participate in several important biological processes such as acid–base balance, respiration, carbon dioxide and ion transport, bone resorption, lipogenesis and electrolyte secretion.[2–6] Many such CA isozymes involved in these processes are important therapeutic targets with the potential to be inhibited/activated for the treatment of a range of disorders such as edema, glaucoma, obesity, cancer, epilepsy, and osteoporosis.[2,6]

Our group and Supuran's group recently investigated the interaction of CA I and II isozymes with several types of phenols, such as hydroxy-/methoxysubstituted benzoic acids as well as di-/trimethoxy benzenes, natural and unnatural bromophenols and several of its substituted derivatives, for example, salicyclates and some of their derivatives.[4–9] In the current research, the natural product **4** is also a diarylmethane derivative (Fig. 1) and an enantiomer. The syntheses of **4** and its racemic derivatives were important and potentially may have biological activities. Therefore, **4** and its derivatives were synthesized and their biological properties were investigated. As CA inhibitors (CAIs) are valuable molecules for therapeutic and pharmacologic applications, we have evaluated these bromophenol derivatives as novel CAIs.

We have purified human CA I, II, IV and VI (hCA I, hCA II, hCA IV and hCA VI) isoenzymes and examined the in vitro inhibition effects of some phenolic, bisphenol, methoxy and bromophenol

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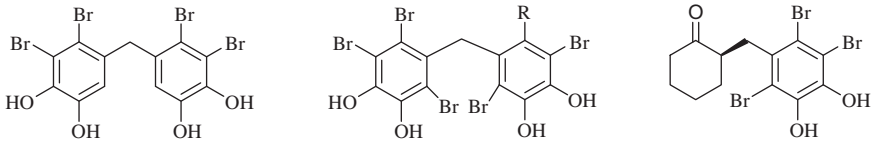
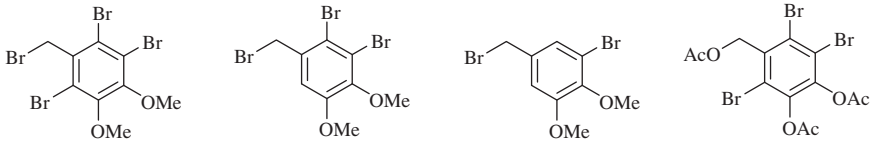


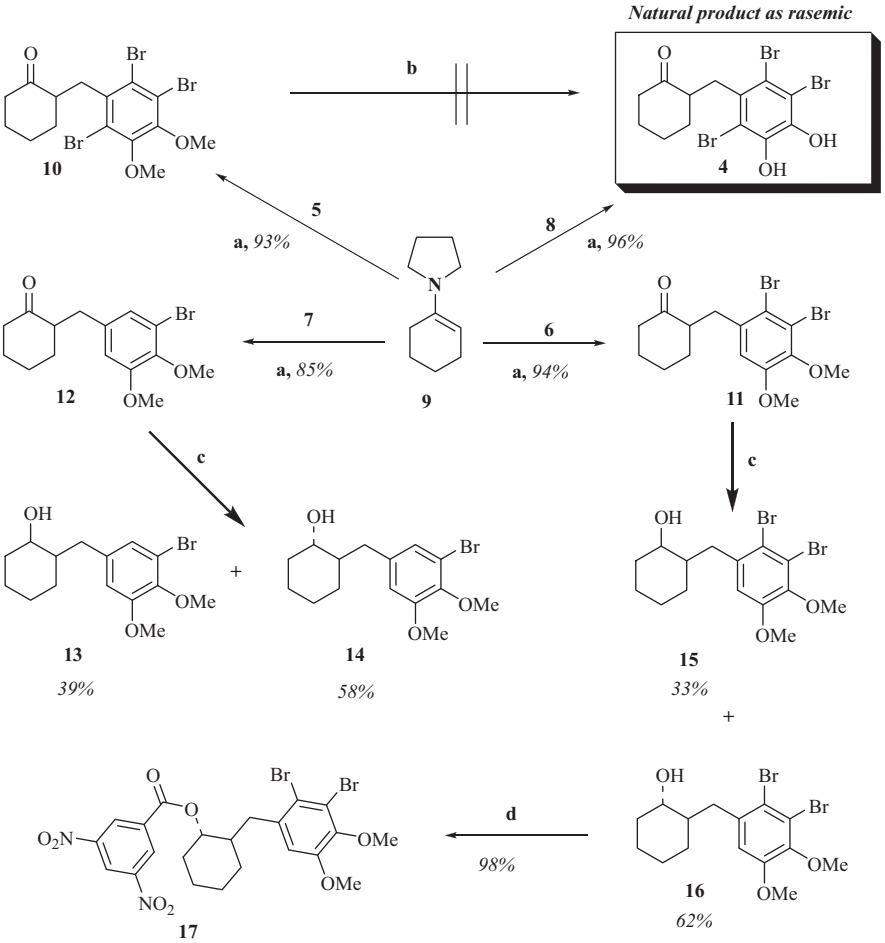
Figure 1. Some naturally occurring bromophenols.



Scheme 1. Prepared some reagents.[1g,14]

compounds mentioned above on these enzymes, using the esterase activity of hCA I, hCA II, hCA IV and hCA VI, with 4-nitrophenyl acetate as substrate.

Natural product **4** is a benzyl group substituted product at the α-carbon atom of cyclohexanone. Compound **4** and its derivatives may be synthesized by a substitution at this carbon of cyclohexanone. For this purpose, reagents tetrabromide **5**, tribromide **6** and dibromide **7** were prepared from their starting materials and related reactions (Scheme 1 and Scheme 2).[14] Enamine **9** was synthesized from cyclohexanone and pirrolydine because enamines can be



Scheme 2. Reagents and conditions: (a) (i) Reflux in dry dioxane, 18 h, under N_2, (ii) Water, additional 1 h; (b) BBr_3, in CH_2Cl_2, 0 °C to rt, under N_2; (c) $NaBH_4$, in MeOH/diethylether, 0 °C (15 min)–rt (1 (d); (d) 3,5-dintrobenzoylchloride, in CH_2Cl_2, rt, over night.